NON-TECHNICAL ABSTRACT

The development of highly effective drug treatment of human immunodeficiency virus-type 1 (HIV-1), the virus that causes acquired immunodeficiency syndrome (AIDS), has given hope to those individuals infected with this deadly disease. However, recent clinical data demonstrates that the virus is not completely eliminated by current drug treatment, but persists in resistant cellular reservoirs, mainly circulating CD4+ lymphocytes, the primary cell infected by HIV-1. Children, who are typically infected with HIV-1 from their mothers at the time of child-birth, suffer a more rapidly progressive course than their adult counterparts. Unfortunately, prolonged treatment lasting many years with the currently available drugs, resulting in great cost and unavoidable, potentially serious side-effects, may not be benefited by cure.

A new type of treatment based on gene therapy for HIV-1 has already been conducted in a first study of adults, by introducing an anti-HIV-1 gene into circulating lymphocytes, the cells primarily involved in mediating immune responses. Importantly, this study indicated that an HIV-1 gene called RevM10 endowed lymphocytes with a survival advantage. However, because HIV-1 infected lymphocytes have a short survival time, and the gene-modified cells were given to the patients only once, these cells were eliminated over a few months. In order to provide a longer lasting treatment, we would like to introduce the RevM10 gene into the subject's blood-forming stem cells from bone marrow, and then re-infuse them. These stem cells are present in bone marrow, give rise to all the cells of blood including lymphocytes, and are retrievable by harvesting them from the bone marrow under general anesthesia. The gene insertion is actually done in tissue culture dishes in the laboratory. Once inserted into a stem cell, the gene is faithfully passed on to all the cells that develop from the gene-modified stem cell after returning it to the subject by intravenous infusion. Gene therapy for HIV-1 will require gene insertion of RevM10 into a sufficient number of the subject's stem cells so that the lymphocytes developing from the gene-modified stem cells are resistant to HIV-1 infection, and accumulate over time.

We will determine in this study whether using a gene therapy approach in children is safe and feasible, with a secondary aim addressing the prospect of benefit. We will treat twelve children, from the ages of three to thirteen, infected with HIV-1. Bone marrow will be collected from the children under general anesthesia, processed in the laboratory to introduce the RevM10 gene to blood stem cells, followed by return of the cells to the subjects by intravenous infusion. Retroviruses which have been engineered to contain the gene active against HIV-1 and to be unable to multiply in the body (called gene "vectors"), will deliver the RevM10 gene to the stem cells. Two different gene vectors will be used side-by-side, to see if the one with the active gene actually works better than the inactive one. The children will be maintained on anti-HIV-1 drugs

throughout the course of the study, because they are known to be effective against the virus. We will examine blood samples taken periodically for the two years of active study to evaluate side-effects from the procedure, whether the RevM10 gene is present in blood cells, and whether this gene provides survival advantage to those lymphocytes containing it. If the RevM10 gene is present and active at sufficient level, it is anticipated that lymphocytes with a survival advantage will accumulate. Potentially, accumulation of sufficient cells will allow for a clinically relevant benefit, that of improvement of immune system function from gene-modified cells.

This study will provide information on the safety, feasibility and usefulness of this approach applying gene therapy for HIV-1 in children. Ideally, it may lead to a new treatment for this disease based on a single therapeutic intervention, with potentially less toxicity and less cost than current therapy.